Carbon Disulfide

The September 1998 issue of *EHP* contained two articles about the neurotoxicity of carbon disulfide. The "NIEHS News" article (*1*) reported on a collaborative study that involved scientists from the NIEHS (Research Triangle Park, NC), the U.S. Environmental Protection Agency (Research Triangle Park, NC), the University of North Carolina (Chapel Hill, NC), Duke University (Durham, NC), and Vanderbilt University (Nashville, TN). In this study, the neurotoxicity of carbon disulfide was detailed from the earliest molecular alterations to neurobehavioral findings to electrophysiologic and morphologic changes, and the utility of intramolecular cross-linking in hemoglobin as a biomarker was defined. I was pleased to read this report, and even more pleased to have participated in this study, but I was distressed to see the cover story in the same issue.

"Multiple System Atrophy Following Chronic Carbon Disulfide Exposure" (*2*), in the "Grand Rounds in Environmental Medicine," is a case report of an individual who developed a degenerative nervous system disease, olivopontocerebellar atrophy, and who had been chronically exposed to carbon disulfide while working for 34 years in a viscose rayon plant in the United States. Frumkin (*2*) concluded, "While this association has not previously been reported, it is clinically and pathologically consistent with a range of movement disorders seen in the setting of occupational carbon disulfide exposure."

Frumkin never saw this patient, nor was he consulted by the patient's physicians during the course of this disease; he only reviewed the medical records and diagnostic studies as an expert witness for the plaintiff in a case that failed to convince a Texas jury that a cause-and-effect relationship existed between carbon disulfide exposure and this man's disease (*3*). I also reviewed this material and concluded that such a relationship was not even remotely plausible; indeed, I thought that there were excellent reasons to conclude that his disease bore no relationship to the exposure. Thus, the publication of this paper raises several concerns: Why did Frumkin feel authorized to publish this report, and were the editors informed about his relationship to this case? Was the paper reviewed by experts in neurotoxicology, clinical neurology, and neuropathology? Will readers conclude that carbon disulfide causes multisystem atrophy? How many more lawsuits will be filed alleging that since B followed A, A caused B, and how many more physicians will reach this vacuous conclusion?

The individual described in this paper (*2*) had classical olivopontocerebellar atrophy, beginning with cerebellar ataxia and progressing over years to involve long tracks and cranial nerve nuclei in the pons. Neither the cerebellum nor the pontine nuclei are affected in carbon disulfide toxicity. However, Frumkin pointed out that olivopontocerebellar atrophy is part of a spectrum of diseases termed multisystem atrophy, which also includes striatonigral degeneration, a disease characterized by clinical parkinsonism. Although extrapyramidal involvement in carbon disulfide toxicity has been alleged in the clinical literature (*4–11*), the only experimental studies reporting lesions in the extrapyramidal system were published over 50 years ago and involved uncontrolled exposures to carbon disulfide that resulted in repeated apneic episodes and confounding hypoxia (*12–14*). Extrapyramindal lesions have never been observed in modern experimental studies, nor did the patient in Frumkin's report (*2*) manifest extrapyramidal signs. On the other hand, the most sensitive structure in the nervous system to carbon disulfide-induced damage is the axon, and this patient never developed evidence for an axonopathy at any time during his career or during his terminal illness. Thus Frumkin's statement that the patient's course of illness was clinically and pathologically consistent with carbon disulfide toxicity has no basis in fact.

Although it certainly was impressive to see an MRI scan on the cover of *EHP*, this paper is not based in either strong science or competent clinical medicine. We depend upon physicians who practice occupational and environmental medicine to apply the science of toxicology to the evaluation and treatment of patients who have been exposed to toxicants. When the exposure involves an agent whose toxicity has never been suspected, case reports have value in alerting physicians and the public to possible dangers. Considerable caution must be exercised, however, in assigning cause-and-effect relationships between toxicants and disease, especially when the agent in question has been in use for many decades, has been studied extensively, and has been subjected to strict regulatory standards.

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References and Notes

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Carbon Disulfide: Frumkin's Response

Graham offers four discrete arguments against an association between carbon disulfide and olivopontocerebellar atrophy. First, he holds that olivopontocerebellar atrophy is clinically incompatible with carbon disulfide toxicity because carbon disulfide toxicity does not affect the cerebellum or pontine nuclei. Second, he asserts that the experimental studies showing extrapyramidal involvement in carbon disulfide toxicity relied on high-dose exposures at levels sufficient to cause apnea. Third, he is concerned that this experimental literature is over 50 years old. Fourth, he argues that the axon is more sensitive to carbon disulfide toxicity than are other parts of the nervous system, suggesting that the absence of axonopathy rules out carbon disulfide toxicity. Graham presents these arguments as ex cathedra pronouncements and cites no basis for any of them. In fact, each is contradicted by available evidence.

With regard to cerebellar involvement in carbon disulfide toxicity, Graham is factually incorrect. Autopsy studies in humans with carbon disulfide toxicity are regrettably rare, but at least two have shown clear evidence of cerebellar involvement (*1,2*). The animal toxicology is far more extensive and has been reviewed in detail (*3–5*); numerous reports show cerebellar involvement in diverse species including rats (*6*), rabbits (*7*), dogs (*8*), and cats (*9*). In fact, carbon